

Adjuvant low-dose interferon α 2a with or without dacarbazine compared with surgery alone: a prospective-randomized phase III DeCOG trial in melanoma patients with regional lymph node metastasis

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Received 5 March 2007; revised 25 July 2007, 1 November 2007 and 26 December 2007; accepted 26 December 2007

Background: More than half of patients with melanoma that has spread to regional lymph nodes develop recurrent disease within the first 3 years after surgery. The aim of the study was to improve disease-free survival (DFS) and overall survival (OS) with interferon (IFN) α 2a with or without dacarbazine (DTIC) compared with observation alone.

Patients and methods: A total of 444 patients from 42 centers of the German Dermatologic Cooperative Oncology Group who had received a complete lymph node dissection for pathologically proven regional node involvement were randomized to receive either 3 MU s.c. of IFN α 2a three times a week for 2 years (Arm A) or combined treatment with same doses of IFN α 2a plus DTIC 850 mg/m² every 4–8 weeks for 2 years (Arm B) or to observation alone (Arm C). Treatment was discontinued at first sign of relapse.

Results: A total of 441 patients were eligible for intention-to-treat analysis. Kaplan–Meier 4-year OS rate of those who had received IFN α 2a was 59%. For those with surgery alone, survival was 42% (A versus C, $P = 0.0045$). No improvement of survival was found for the combined treatment Arm B with 45% survival rate (B versus C, $P = 0.76$). Similarly, DFS rates showed significant benefit for Arm A, and not for Arm B. Multivariate Cox model confirmed that Arm A has an impact on OS ($P = 0.005$) but not Arm B ($P = 0.34$).

Conclusions: 3 MU interferon α 2a given s.c. three times a week for 2 years significantly improved OS and DFS in patients with melanoma that had spread to the regional lymph nodes. Interestingly, the addition of DTIC reversed the beneficial effect of adjuvant interferon α 2a therapy.

Key words: adjuvant treatment, dacarbazine, immunotherapy, interferon α , melanoma

introduction

Cutaneous melanoma continues to be a major health problem in Caucasian populations. Its incidence is increasing faster than that of any other malignancy and it often affects younger patients [1, 2]. Once distant metastasis develops, melanoma is almost always fatal, with an estimated median survival range of 6–12 months and a 5-year survival rate of ~5% [3, 4]. However, in patients with melanoma that has spread to the regional lymph nodes without recognizable further

metastasis, cure rates of up to 50% have been reported [4]. Considerable effort has been expended in attempts to identify new active adjuvant treatment strategies for such patients with high-risk melanoma before they develop visceral metastases [5, 6].

A number of randomized trials have investigated the role of interferon alpha (IFN α) as adjuvant therapy for high-risk melanoma in stage II (primary melanoma with a tumor thickness with >1.5 mm) [7, 8] and in stage III disease (melanoma with spread to the regional lymph nodes with or without skin metastases) [9–14]. Some of the adjuvant interferon trials suggest a benefit at least for a prolongation of disease-free survival (DFS) for IFN α , others showing no statistically significant differences. Thus, there is a need for more data to be accrued before definitive conclusions on the role of adjuvant IFN α treatment in high-risk melanoma can be reached [15].

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In spite of many other attempts to develop effective adjuvant therapy for patients with high-risk melanoma, IFN α remains the only agent which has demonstrated some therapeutic activity. Dacarbazine (DTIC) chemotherapy has been examined in the adjuvant setting in several trials and provided no survival benefit, neither as a single agent nor in combination with Bacille Calmette–Guerin or other nonspecific immunotherapy [16–18]. In contrast, in melanoma patients with distant metastasis, a meta-analysis on the combination of DTIC and IFN α seemed to reveal higher response rates than single-agent DTIC, but without a clear impact on a prolonged survival [19–21]. Therefore, we examined the combination of IFN α plus DTIC as an option to improve adjuvant treatment results.

The primary goal of the present trial was the improvement of overall survival (OS), and secondary end points were prolongation of recurrence-free survival and occurrence of adverse events. In addition, health-related quality of life (QoL) was measured by a questionnaire.

methods

patients

From February 1997 to September 2001, 444 patients with primary melanoma that had spread to the draining lymph nodes were recruited into a randomized clinical trial. The patients were treated at 42 centers belonging to the Dermatologic Cooperative Oncology Group (DeCOG) network in Germany and Switzerland (see appendix). The trial protocol was approved by the central ethics committee of the University Medical Center Tuebingen, Germany, and by ethics committees at all other participating centers.

Patients with primary cutaneous malignant melanoma and pathologically proven regional node metastases (either microscopic or macroscopic metastasis) were eligible to enter the study. Only patients with a complete lymphadenectomy and absence of satellite-, in-transit, or distant metastases were eligible. Other inclusion criteria were age between 18 and 75 years' absence of any other malignant disease apart from basal cell carcinoma; and absence of cardiac, liver, renal, neurological, or autoimmune diseases. Neither previous exposure to IFN α , concomitant use of corticosteroids, nor other investigational drugs were allowed. Written informed consent was obtained from each patient before entry into the study. A complete medical history, physical examination, and laboratory tests (including blood count, chemistry profile, and urine analysis) were obtained. All patients had at least a chest radiograph and abdominal ultrasound or computed tomography (CT) scans to exclude metastatic spread beyond the draining lymph nodes.

study design

Metastatic spread to the regional lymph nodes was detected either clinically at primary melanoma diagnosis or during follow-up examinations or by means of sentinel lymph node biopsy. Radical dissection of the involved regional lymph node basin was carried out before randomization, according to the German guidelines on the treatment of melanoma. Patients were randomly assigned to receive adjuvant IFN α 2a alone (Arm A), adjuvant IFN α 2a plus DTIC (Arm B), or observation alone (Arm C). The aim of the trial was to assess the efficacy and toxicity of Arm A and Arm B versus Arm C. The main end point for efficacy was melanoma-specific survival. A fax randomization was carried out at the University Medical Center Tuebingen according to a permuted block randomization list, and no stratification was employed. Figure 1 shows the trial profile.

Patients randomly assigned to receive IFN α 2a were given 3 MU s.c., three times a week, and patients in the combined Arm B additionally received

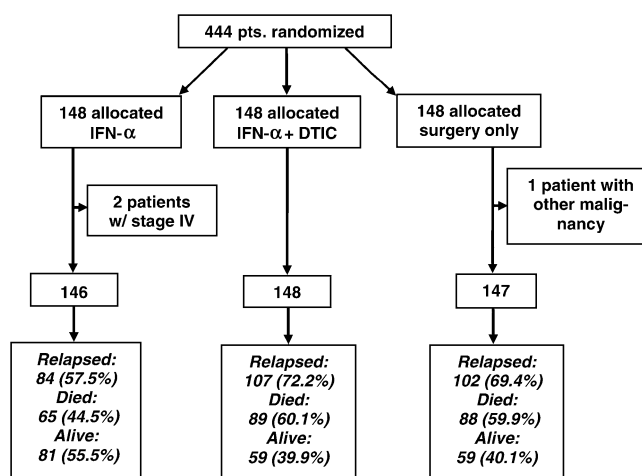


Figure 1. Trial profile. In each study arm there have been recorded three nonmelanoma-related cases of death and these are included in the number of deaths given here.

DTIC 850 mg/m² via i.v. infusion (20 min) on day 1 every 28 days during the first 6 months, every 42 days during months 7–12, and every 56 days during months 13–24. DTIC was administered in a light-protected infusion system. All patients treated with IFN α 2a routinely received paracetamol (2 × 500 mg) after the injection. Patients treated with DTIC received an antiemetic treatment with setrones (tropisetron or ondansetron). Treatment started within 6 weeks after removal of the lymph node metastases and continued for 2 years. We discontinued treatment if a patient developed severe or life-threatening adverse events thought to be caused by IFN α 2a or by DTIC, or if local or distant metastases were detected. Grade 4 toxic effects required permanent withdrawal of treatment. Grade 3 toxic effects allowed subsequent treatment to be reintroduced at reduced dosage levels (half dosage for interferon and DTIC was recommended). Follow-up examinations took place every 3 months during the entire study period or at any time when symptoms developed. At a 3 years follow-up after the end of therapy, patients had complete clinical examination, blood tests, and lymph node ultrasound and every 6 months chest radiograph and abdominal ultrasound or CT scans. The study was monitored using on-site visits carried out by the DeCOG study center in Tuebingen and independently audited by three academic clinical study centers.

Health-related QoL was measured using a standardized questionnaire developed by the European Organisation for Research and Treatment of Cancer (EORTC) (QLQ-C30, Version 2.0) which is specifically tailored for cancer patients [22]. The questionnaire was filled in every 3 months at the follow-up examinations during the treatment period.

statistical methods

The study was designed to detect a treatment effect difference of 15% in the 4-year survival rate at $\alpha = 0.05$ (estimates: observation group 25% versus treatment groups 40%), with a power (1 – β) of 0.80 on the basis of one-sided testing. The sample size calculation required 134 assessable patients per study arm, and assuming 10% dropouts for each arm, 148 patients had to be included (total: 444 patients). Evaluation of the QLQ-C30 questionnaire has been carried out according to the recommendations of the EORTC [22]. Patients' characteristics in the different study arms and the QoL scores were tested for differences by the chi-square test and the Kruskal–Wallis test. Intention-to-treat population comprised all randomly assigned patients who were eligible for this study. Per-protocol population comprised eligible patients treated according to protocol; follow-up of

patients with protocol violations was censored at the time of withdrawal from the study. Follow-up of patients who died without relapse was censored at the date of death. To calculate OS in the study arms, Kaplan–Meier estimates were generated. Only deaths from melanoma were included into the survival analysis. Survival times were calculated from the date of randomization. Comparison of survival curves were drawn by log-rank test. Additionally, Cox proportional hazards model was used to identify important prognostic factors. Proportional hazards assumption was assessed by the plot of the Schoenfeld residuals against time. Significance of covariates was measured with the likelihood ratio test, and the role of each covariate entering the model was assessed by the Wald statistic. Survival plots were carried out according to the recommendations of Pocock and colleagues [23] and the study report has been elaborated according to the CONSORT statement [24]. Statistical analyses were carried out with the statistical software SPSS 11.5 (SPSS Inc., Chicago, IL) and “The R Project for Statistical Computing” version 1.8.0.

results

A total of 148 patients were randomly assigned to each of the study arms (total 444) and 441 patients were eligible for the intention-to-treat analysis (Figure 1). Table 1 shows the characteristics of these patients. The study arms were well balanced for all relevant prognostic factors for stage III melanoma patients. Median follow-up time was 47 months. The 4-year OS rate in patients who received single-agent INF α 2a was 59% compared with 42% for those who had a lymph node dissection only (Table 2 and Figure 2). The differences between the Kaplan–Meier melanoma-specific survival curves were significant ($P = 0.0045$). There was no significant difference between patients who received combined treatment with INF α 2a and DTIC with a 4-year OS rate of 45% compared with untreated controls ($P = 0.75$). In each study arm, there were only three patients with nonmelanoma-related deaths, and if they are considered as events as well, the treatment comparisons remained practically identical. Similar results were found for 4-year recurrence-free survival rates (RFS) with 39% for patients with single-agent INF α 2a versus 27% RFS for patients with surgery alone ($P = 0.018$) and 29% for patients with combined treatment ($P = 0.97$) (Table 2 and Figure 3). The survival curve of patients treated with the combination of INF α 2a and DTIC virtually overlaps with the survival curve of patients treated with surgery alone, indicating that DTIC reverses beneficial effects of adjuvant INF α treatment. In all, 420 of 441 patients (95%) received treatment per protocol, and only 21 patients (Arm A 14; Arm B 4, and Arm C 3 patients), who withdraw their informed consent and received different treatments as planned, were classified as protocol violators. The significant differences of the intention-to-treat analysis were confirmed by the per-protocol analysis (data not shown). Protocol violators and patients with nonmelanoma-related deaths were both included into the intention-to-treat analysis.

Table 3 shows a multivariate analysis of prognostic factors. Patients with macroscopic involvement had a worse prognosis (hazard ratio = 2.4, $P < 0.0001$) than those with microscopic node involvement (sentinel node positivity). Furthermore, patients with two to four and more than four positive nodes had a worse outcome than those with one node only.

Table 1. Patients' characteristics

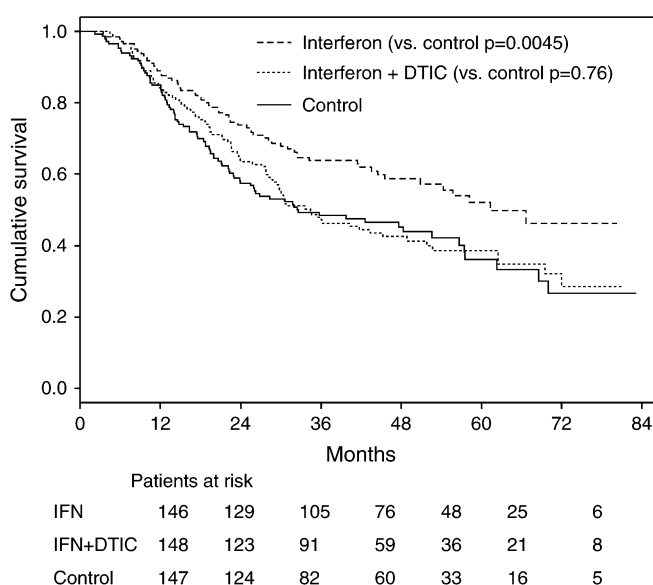
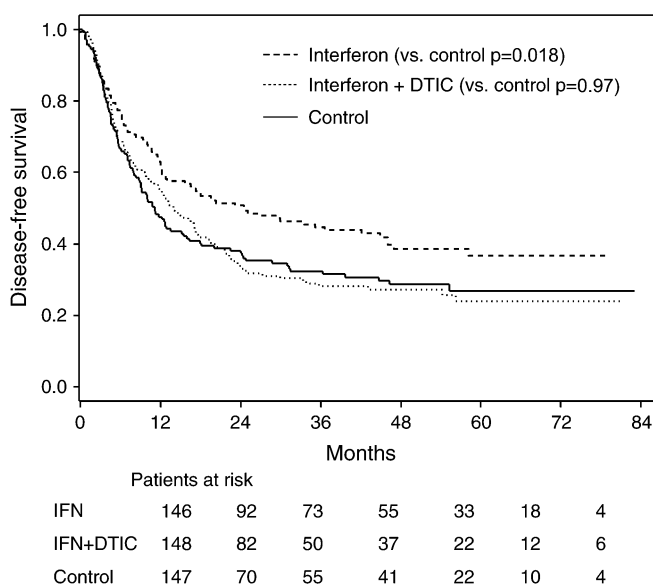
Characteristics	Interferon (n = 146)	Interferon plus dacarbazine (148)	Surgery only (n = 147)
Sex			
Male	92 (63%)	93 (63%)	85 (58%)
Female	54 (37%)	55 (37%)	62 (42%)
Age (years)			
0–40	29 (20%)	28 (19%)	27 (19%)
41–50	20 (14%)	30 (20%)	33 (23%)
51–60	48 (33%)	40 (27%)	33 (23%)
>60	49 (33%)	50 (34%)	52 (38%)
			Two missing
Breslow depth of primary melanoma (mm)			
<1.5	45 (31%)	35 (24%)	36 (25%)
1.51–3	40 (27%)	49 (33%)	53 (36%)
3.01–4	13 (9%)	19 (13%)	16 (11%)
>4	30 (21%)	30 (20%)	28 (19%)
Not assessed	18 (12%)	15 (10%)	14 (9%)
Clark level			
II	4 (3%)	4 (3%)	5 (3%)
III	33 (23%)	34 (23%)	31 (21%)
IV	72 (49%)	80 (54%)	78 (53%)
V	18 (12%)	12 (8%)	12 (8%)
Not assessed	19 (13%)	18 (12%)	21 (14%)
Site of primary			
Head and neck	12 (8%)	8 (5%)	9 (6%)
Upper limbs	13 (9%)	16 (11%)	21 (14%)
Lower limbs	49 (34%)	48 (33%)	42 (29%)
Trunk	60 (41%)	64 (43%)	63 (43%)
Not otherwise specified	12 (8%)	12 (8%)	12 (8%)
Type of dissection			
Axillary	61 (42%)	71 (48%)	79 (54%)
Groin (inguino-iliac)	63 (43%)	59 (40%)	55 (37%)
Laterocervical	18 (12%)	13 (9%)	10 (7%)
Other sites	4 (3%)	5 (3%)	3 (2%)
Clinical nodal status			
N1a (microscopic involvement)	32 (22%)	32 (22%)	40 (27%)
N1b (macroscopic involvement)	110 (75%)	113 (76%)	103 (70%)
Not otherwise specified	4 (3%)	3 (2%)	4 (3%)
Disease status at entry			
Primary	61 (42%)	66 (45%)	53 (36%)
Recurrent	76 (52%)	74 (50%)	86 (59%)
Not otherwise specified	9 (6%)	8 (5%)	8 (5%)
Number of positive nodes			
1	69 (47%)	76 (51%)	61 (42%)
2–4	50 (34%)	41 (28%)	54 (37%)
>4	12 (8%)	14 (10%)	17 (11%)
Not assessed	15 (10%)	17 (11%)	15 (10%)

Treatment comparison (single-agent INF α 2a versus observation) adjusted for these two variables remained significant ($P = 0.005$).

Toxicity was mild for INF α 2a (Arm A) and for combined treatment with INF α 2a and DTIC (Arm B). Grade 3 and grade 4 adverse events were recorded in 13 patients of the treatment

Table 2. Univariate analysis on overall and disease-free survival

Treatment arm	Hazard ratio	97.5% CI	4-year rate %	97.5% CI
Overall survival				
Surgery only	1.0		42.4	32.9; 52.1
Interferon	0.62	0.42; 0.89	59.0	49.4; 68.6
Interferon plus dacarbazine	0.96	0.67; 1.33	45.2	35.6; 54.8
Disease-free survival				
Surgery only	1.0		27.3	18.8; 35.8
Interferon	0.69	0.49; 0.96	39.0	29.4; 48.6
Interferon plus dacarbazine	1.01	0.72; 1.36	29.4	20.7; 38.1

**Figure 2.** Kaplan-Meier overall survival.**Figure 3.** Kaplan-Meier disease-free survival.

arm with INF α 2a and in 25 patients of the combined arm. Premature termination of treatment due to toxicity or lack of tolerability by the patient occurred in 38 patients, of these 20 patients in Arm A and in 16 patients in Arm B. No significant differences were observed between both treatment arms. The most common side-effects (grades 1–4) were leucocytopenia (Arm A: 25%; B: 43%), nausea and vomiting (A: 15%; B: 40%), elevation of liver enzymes (A: 22%; B: 24%), pain (A: 23%; B: 18%), diarrhea (A: 11%; B: 17%), and fever (A: 11%; B: 15%), and grades 3 and 4 toxicity occurred in <2.5% of patients; Table 4.

The QoL analysis compared the different scores of the EORTC QLQ-C30 questionnaire at baseline and 6 months after randomization in a total of 238 patients. Six-month values were

Table 3. Multivariate analysis on survival (Cox hazard regression model)

Variable	Hazard ratio	Standard error	97.5% CI	P value
Clinical nodal status				
N0 (microscopic involvement)	1.000			
N1b (macroscopic involvement)	2.427	0.197	1.986; 2.868	<0.0001
Nodes				
1 positive	1.000			
2–4 positive	1.490	0.220	0.997; 1.983	0.070
>4 positive	1.335	0.152	0.995; 1.675	0.057
Treatment arm				
Surgery only	1.000			
Interferon	0.609	0.178	0.210; 1.008	0.005
Interferon plus dacarbazine	0.854	0.166	0.482; 1.226	0.343

Table 4. Grade 3 + 4 toxicity

	IFN α		IFN α plus DTIC	
	Grade 3	Grade 4	Grade 3	Grade 4
Anemia	0.8%	–	2.5%	–
Leukopenia	–	–	2.5%	–
Granulopenia	–	–	0.8%	–
Thrombozytopenia	0.8%	–	0.8%	–
Liver enzyme elevation (AP/SGOT)	–	–	0.8%	–
Nausea/emesis	0.8%	–	1.6%	–
Diarrhea	1.6%	–	–	–
Constitutional/fever	–	–	–	–
Allergy	–	–	–	0.8%
Skin	0.8%	–	0.8%	–
Pulmonary	–	–	0.8%	–
Infection	0.8%	–	0.8%	–
Consciousness	1.6%	0.8%	1.6%	–
Peripheral nerves	–	–	0.8%	–
Pain	1.6%	–	1.6%	–

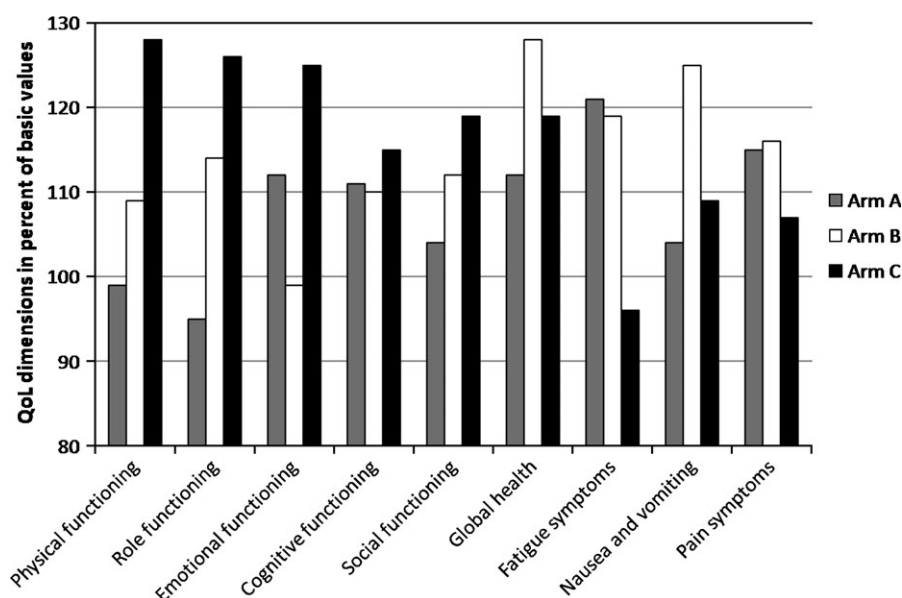


Figure 4. Quality of life (QoL) dimensions at 6 months after randomization. Six-month values were calculated as percent of baseline values and higher values indicate deterioration of QoL.

calculated as percent of baseline values (Figure 4). Interestingly, patients under adjuvant treatment had a better outcome for the general dimensions of QoL as ‘physical functioning’ (Arm A versus Arm C: $P = 0.007$), ‘role functioning’ (Arm A versus Arm C: $P = 0.008$), and ‘emotional functioning’ (Arm A versus Arm C: $P = 0.048$) in comparison to the patients treated with surgery only. However, patients in the adjuvant treatment arms displayed more drug-related symptoms such as the ‘fatigue symptom scale’ (Arm A versus Arm C: $P = 0.036$) and those treated with DTIC also for the ‘nausea and vomiting scale’ (Arm B versus Arm C: $P = 0.037$).

discussion

This clinical trial demonstrated two major findings: (i) melanoma patients with metastatic spread to regional lymph nodes had a significantly improved DFS and OS when they received low-dose single-agent $\text{INF}\alpha 2\alpha$ for 2 years and (ii) patients who were treated with the combination of $\text{INF}\alpha 2\alpha$ and DTIC did not show an improved DFS or OS compared with those with observation alone.

It is an unusual finding in this study that the OS benefit is larger than the DFS benefit. In most other studies the reverse has been observed. The present study is part of a series of smaller studies that have addressed the role of low-dose $\text{INF}\alpha$ and it should be mentioned the possibility that the play of chance may have been a factor in that way, that some trials will underestimate the treatment effect and some will overestimate it. The latter may be true in the present trial.

DTIC was added to $\text{INF}\alpha 2\alpha$ because a meta-analysis in stage IV melanoma patients showed an improvement of the response rates. However, no effect on the OS time was observed [25]. This phase III trial wanted to evaluate the OS time in patients who were treated in the adjuvant setting with $\text{INF}\alpha$ with or

without DTIC compared with observation alone. DTIC reversed the improvement of OS that was achieved in the study arm treated with $\text{INF}\alpha 2\alpha$ alone. Possible explanations are the immunosuppressive effects of DTIC [26, 27] which might counteract the immunostimulatory effects of $\text{INF}\alpha 2\alpha$. In addition, exposure of melanoma cells to DTIC might lead to enhanced tumor growth and metastasis, as evidenced by a recent mouse model [28, 29].

An imbalance of prognostic factors between the treatment groups can be widely excluded as a reason for the survival differences. Particularly, the number of positive lymph nodes, the disease status at study entry, and the nodal status in accordance to the tumor–node–metastasis (TNM) classification [30–32] did not differ significantly between the arms. However, we did not document a possible ulceration of the primary tumor because this was not part of the TNM/American Joint Committee on Cancer classification system at the initiation of this clinical trial. To our best knowledge, there are no patient characteristics which could explain the significant OS and relapse rate differences between single-agent $\text{INF}\alpha 2\alpha$ and the comparator arms. Whereas 60.1% of patients treated with $\text{INF}\alpha$ and DTIC died during the observation period, in the untreated control arm a comparable number (59.9%) deceased. In contrast, only 44.5% of patients treated with single-agent $\text{INF}\alpha 2\alpha$ died due to metastatic melanoma.

The finding of a significant survival improvement for single-agent $\text{INF}\alpha 2\alpha$ compared with surgery alone is difficult to interpret. There are at least four clinical trials, in which patients have been treated with low-dose $\text{INF}\alpha$ for stage III disease [9–12]. These trials were neither able to demonstrate a significant improvement for relapse-free survival nor for OS. Therefore, this clinical trial is in clear contrast to the previously published multicenter trials in the same setting. The reasons are not obvious for us since the selection of patients did not differ

significantly from the other trials. Dosage does not play a significant role as all these clinical trials used low-dose IFN α thrice a week. In a recent publication, Stadler et al. showed that a combined treatment with DTIC and IFN α was associated with improvement of prognosis compared with surgery alone. The schedule utilized in this study was quite different from ours: DTIC and IFN α were not given simultaneously, but DTIC was given for only two cycles and then the IFN α treatment was subsequently added. In this case, the DTIC may not negatively affect the immunological treatment. The study does not test the question whether the application of DTIC adds anything to the effect of IFN α [33].

Recent meta-analyses of 12 adjuvant IFN α trials in high-risk melanoma patients demonstrated that IFN α prolongs recurrence-free survival in a subgroup of melanoma patients. A 17% reduction in the risk of recurrence has been calculated. However, the effect on a prolongation of OS is less convincing with a 7% reduction in the risk of death [15, 34].

It is obvious that most of the clinical trials which have been carried out in the adjuvant treatment of malignant melanoma—including the present study—were underpowered. Therefore, the chance to detect statistical significant differences in DFS or OS is relatively low. A more careful selection of patients who are likely to benefit from adjuvant IFN α is mandatory. Unfortunately, predictive factors for melanoma patients treated with IFN α have not been established yet. Even in a large-sized EORTC trial on 1388 patients with thick primary tumors or regional lymph node metastases only, a small increase (7.2%) in the distant metastases-free interval and a 5.4% improvement in OS have been detected after a median follow-up of 4.65 years. The differences were not statistically significant [35].

In conclusion, adjuvant INF α 2a treatment with low dosages in a homogenous group of patients with first manifestation of metastasis in regional lymph nodes improved DFS and OS. However, the combination of INF α 2a with the cytotoxic agent DTIC reversed this beneficial effect in this randomized trial. Although only 444 patients have been randomized, the results are remarkable since they reached statistical significance due to the impressive different numbers in the death and relapse rates. There are no obvious reasons to believe a bias between the groups, but the impact of INF α in the adjuvant treatment of melanoma remains controversial due to heterogeneous results in the literature. Most likely, no further large-sized clinical trials on conventional IFN α will be initiated since multinational trials on pegylated INF α 2a and pegylated INF α 2b are already underway in the adjuvant treatment of high-risk melanoma patients.

funding

German Cancer Aid (Deutsche Krebshilfe); German Cancer Society (Frankfurt, Germany); Hoffmann-LaRoche AG (Grenzach-Whylen, Germany).

acknowledgement

All authors participated in design, execution, and analysis of the report.

appendix: Participating centers and investigators

Centers	Investigators
Berlin Neukölln	B Hermes, P Kohl
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Bremen	F Bahmer
Buxtehude	P Mohr
Chemnitz	HJ Koch
Demmin	B Rosenbaum
Dessau	Y Kröning, HD Göring
Detmold	FW Kleinsorge
Dortmund	R Herbst, P Frosch
Dresden	G Hansel, U Wollina
Dresden	A Stein, G Sebastian, M Meurer
Duisburg	J Kunze,
Düsseldorf	KW Schulte, T Ruzicka
Erfurt	I Kellner, R Linse
Essen	S Esser, M Goos
Flensburg	JG Saal
Frankfurt/M.	D Rinne, C Spieth, R Kaufmann
Hamburg St. Georg	M Weichenthal
Hamburg UKE	K Neuber, I Moll
Hannover	R Gutzmer, A Kapp
Hildesheim	I Schubert-Knopplik, F Vakilzadeh
Homburg/Saar	C Pföhler, U Reinhold, W Tilgen
Jena	K Karte, M Kaatz, P Elsner
Kiel	M Möller, A Hauschild
Köln	A Jöckel, C Mauch, T Krieg
Leipzig	B Pfeil, UF Hornstein
Lemgo	RPA Müller
Ludwigshafen	L Köhler, V Voigtländer
Magdeburg	J Ulrich, G Gollnick
Mannheim	S Ugurel, D Schadendorf
Meran	Z Pierfrancesco, E Vigl
Minden	C Hartig, J Böttjer, R Stadler
München	MH Schmidt-Wendtner, M Volkenandt
Münster	M Schiller, D Nashan, T Luger
Norderstedt	R Hoffmann
Nordhausen	K Knabner
Oldenburg	P Pelzer, E Hölzle
Regensburg	B Coras, W Stolz
Rostock	R Zimmermann, G Groß
Tübingen	P Radny, UM Caroli, C Garbe
Zürich	L Heinzerling, R Dummer
Zwickau	B Knopf

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